12, 14, 16, 39-41, 43, 44, and 46 are rejected under 35 U.S.C. §102(b). Claims 1, 10, 12, 13, 15, 16, 39, and 44-46 are rejected under 35 U.S.C. §102(e). Claims 1, 2, 7-9, 10-11, 15, and 39-44 are rejected under 35 U.S.C. §103(a). The disclosure is also objected to because of informalities relating to Tables 5 and 6. Entry of the amendment, reconsideration of the rejection, and allowance of all pending claims are requested.

The Amendment

Claims 1, 5, 6, 7, 18, 20, 33, 38, 39 and 41 have been amended. The amended claims are supported by the application as filed.

Claim 1 has been amended to replace "an inducible promoter" with "a heat shock promoter". Claim 1 has further been amended to specify that the conditions that activate the inducible promoter are hyperthermic conditions comprising a temperature between about 37°C and about 42°C. Support for this amendment can be found on page 3, line 20-26; page 4, line 1-19; page 14, lines 3-14; page 16, lines 15-27; and page 17, lines 1-4. Additional support for this amendment can be found on pages 14-18 (see "Heat Shock Response" and "Hyperthermia Therapy").

Claims 5, 6 and 7 have been amended to depend upon claim 1. Support for this amendment can be found on page 4, lines 13-16 and page 33, lines 12-15.

Claim 18 has been amended to replace "an inducible promoter" with "a heat shock promoter". Claim 18 has also been amended to specify that the conditions under which the heat shock promoter is activated are hyperthermic conditions comprising a temperature between about 37°C and about 42°C. Support for this amendment can be found on page 6, lines 9-22 and page 14, lines 1-14. Additional support for this amendment can be found on pages 14-18 (see "Heat Shock Response" and "Hyperthermia Therapy").

Claim 20 has been amended to depend upon claim 18. Support for this amendment can be found on page 6, lines 18-20; page 12, lines 21-24; and page 13, lines 5-9.

Claim 33 has been amended to replace "an inducible promoter" with "a heat shock promoter". Further, claim 33 has been amended to specify that the conditions under which the heat shock promoter is activated are hyperthermic conditions comprising a temperature between about 37°C and about 42°C. Support for this amendment can be found on page 8, lines 3-20; page 14, lines 3-14; and page 57, lines 15-26. Additional support for this amendment can be found on pages 14-18 (see "Heat Shock Response" and "Hyperthermia Therapy").

Claim 38 has been amended to replace "an inducible promoter" with "a heat shock promoter". Support for this amendment can be found on page 8, lines 21-27; page 9, lines 1-8; and page 18, lines 1-16. Claim 38 has further been amended to clarify that a second promoter is operably linked to "a" selected polynucleotide to comply with the Examiner's suggestion that claim 38 is rendered vague and indefinite by the phrase "said selected polynucleotide" on line 5, as there is no previous recitation of a selected polynucleotide.

Claim 39 has been amended to replace "an inducible promoter" with "a heat shock promoter". Further, claim 39 has been amended to specify that the heat shock promoter is activated at hyperthermic conditions comprising a temperature between about 37°C and about 42°C. Support for this amendment can be found on page 8, lines 21-27; page 9, lines 1-5; and page 18, lines 1-25. Additional support for this amendment can be found on pages 14-18 (see "Heat Shock Response" and "Hyperthermia Therapy").

Claim 41 has been amended to depend upon claim 39. Support for this amendment can be found on page 4, lines 13-16 and page 33, lines 12-15.

Entry of the amendments is respectfully requested.

Rejections Under 35 U.S.C. §112

Claims 1, 2, 7, and 39-41 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. With regard to this rejection, the Examiner holds that the specification does not disclose the source of the promoters and does not disclose any sequence data associated with the heat shock promoters HSP28, HSP72 or HSP73. The Examiner further states that the limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of promoter regions of HSP28, HSP72 or HSP73, at the time the application was filed.

The rejection is respectfully traversed.

Claim 1 is directed to a method of effecting expression of a selected polynucleotide in a mammalian cell which includes providing an expression construct with a heat shock promoter linked to a gene encoding a transactivating factor, and a second promoter linked to the selected polynucleotide, wherein the second promoter is activated by the transactivating factor. The method further includes introducing the expression construct into the cell and subjecting the cell to conditions which activate the promoter, resulting in the expression of the selected polynucleotide. Applicants have amended claim 1 to specify that the inducible promoter is a heat shock promoter. Applicants have further amended claim 1 to specify that the conditions that activate the heat shock promoter are hyperthermic conditions comprising a temperature between about 37°C and 42°C. Claim 2 has been canceled. Claims 5, 6 and 7 depend upon amended claim 1. Claim 39 is directed to an expression product, including a gene encoding a transactivating factor, a heat shock promoter linked to the gene, a selected polynucleotide, and a second promoter linked to the selected polynucleotide, wherein the second promoter is activated by the transactivating factor. Applicants have amended claim 39 to specify that the inducible promoter is a heat

shock promoter that is activated at hyperthermic conditions comprising a temperature between about 37°C and 42°C. Claim 40 has been canceled. Claim 41 has been amended to depend upon amended claim 39.

In the office action, the Examiner states that while it is evident that cDNAs encoding hsp28, hsp72, and hsp73 proteins have been previously isolated and characterized before the time of filing of the instant invention, a search of the patent and non-patent literature databases has not revealed any references disclosing particular promoter regions of HSP28, HSP72 or HSP73. Applicants have extensively described various promoters and promoter control regions (see page 29, section: f) Control Regions) and the use of the HSP70 promoter in order to induce expression of a reporter gene (see page 58, Example 1). Thus, Applicants assert that the skilled artisan would not only be fully capable of recognizing what is claimed in the instant invention but also be capable of producing the claimed expression construct wherein the heat shock promoter is HSP28, HSP72 or HSP73, by following the written guidelines provided in Applicants' specification. "An objective standard for determining compliance with the written description requirement is, '[D]oes the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.' *In re Gosteli,* 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar,* 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed." (MPEP 2163.02) "The examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." 541 F.2d at 265. 191 USPQ at 98. See also *Ex parte Sorenson,* 3 USPQ2d 1462, 1463 (Bd. Pat. App. & Inter. 1987)." (MPEP 2163.04)

The Examiner appears to imply that none of Applicant's explicit teachings and general guidelines with respect to HSP70 is applicable to HSP28, HSP72 or HSP73. Applicants assert that the guidelines

provided in the specification are more than sufficient in order for the skilled artisan to recognize that Applicants were in possession of the necessary common features of the elements possessed by HSP70, HSP90, HSP60, HSP27, HSP72, HSP73, HSP25, ubiquitin, and HSP28, as disclosed in the present invention. In addition, Applicants disagree with the Examiner's assertion that there are no references disclosing particular promoter regions of HSP28, HSP72 or HSP73. Applicants point the Examiner to Hastie *et al.* (*Lung* 1997, 175:287-98) who disclose that the promoter of the gene encoding the 72-kDa heat shock protein has an element responsive to cAMP, which may be affected by beta-agonists. Hastie *et al.* found that albuterol *in vitro* increased the levels of Hsp72 and Hsp73 in epithelial cells from either nonpremedicated or placebo-treated donors and concluded that beta-agonists elevate or prolong an elevated stress response in epithelial cells, possibly through cAMP-mediated effects. Further, Zhou *et al.* (*J. Invest. Dermatol.* 1998, 111:194-8) report that following UV exposure, the heat shock transcription factor 1 (HSF1) dissociated from HSP72-HSF1 complexes, underwent trimerization and phosphorylation, and demonstrated DNA binding activity to the heat shock element in the promoter region of the hsp72 gene. In addition, Lee *et al.* (*Biochem. Pharmacol.* 1996, Jul 26, 52:311-9) investigated the effect of 1 alpha-25-dihydroxyvitamin D3 [1,25-(OH)2D3] on the expression of the 28-kDa heat shock protein gene (hsp28) and the protein kinase C beta gene (PKC beta). Their results suggest that the dual effect of 1,25-(OH)2D3 on hsp28 and PKC beta gene expression may be due to the different sequence composition of the vitamin D response element in the promoter region as well as an accessory factor for each gene. Thus, Applicants respectfully assert that references exist that discuss promoter regions of HSP28, HSP72 or HSP73.

In light of the amendments and arguments presented, Applicants respectfully request that the rejection of claims 1, 5, 6, 7, 39 and 41 under 35 U.S.C. §112, first paragraph be withdrawn.

Claims 1-15, and 17-38 are rejected under 35 U.S.C. §112, first paragraph. The Examiner states that the specification, while being enabling for an expression construct comprising the inducible promoters,

HSP70, HSP90, HSP60, HSP27, and HSP25, and ubiquitin, does not reasonably provide enablement for expression constructs comprising the inducible promoters, HSP28, HSP72, or HSP73 or methods of using the expression constructs comprising these promoters. The Examiner holds that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

This rejection is respectfully traversed.

Applicants have amended claim 1 to specify that the inducible promoter is a heat shock promoter. Applicants have further amended claim 1 to specify that the conditions that activate the heat shock promoter are hyperthermic conditions comprising a temperature between about 37°C and 42°C (*supra*). Claims 2-4 have been canceled. Claims 5-15 and 17 depend upon amended claim 1. Claim 18 is directed to a method of providing a subject with a therapeutically effective amount of an expression product of a selected polynucleotide, including providing a first expression construct with an inducible promoter linked to a transactivating factor; providing a second expression construct with a promoter linked to the selected polynucleotide, wherein the second promoter is activated by the transactivating factor; introducing the first and second expression construct into a cell of the subject; and subjecting the cell to conditions which activate the inducible promoter, wherein the expression of the selected polynucleotide is induced by the conditions. Applicants have amended claim 18 to specify that the inducible promoter is a heat shock promoter and that the conditions the cell is subjected to are hyperthermic conditions comprising a temperature between about 37°C and 42°C. Claims 19 and 22-26 depend on amended claim 18. Claim 20 has been amended to depend on amended claim 18. Claim 21 depends on amended claim 20. Claims 27-32 have been canceled. Claim 33 is directed to a method of provoking an immune response in a mammal, including providing an expression construct with an inducible promoter linked to a gene encoding a transactivating factor, and a second promoter linked to a selected polynucleotide, wherein the second

promoter is activated by the transactivating factor; introducing the expression construct into a mammal; and subjecting the cell to conditions which activate the inducible promoter, wherein the conditions result in the expression of the selected polynucleotide and the expression product of the selected polynucleotide is expressed in an amount effective to provoke an immune response in the mammal, the immune response being selected from the group consisting of humoral immune response and a cellular immune response. Applicants have amended claim 33 to specify that the inducible promoter is a heat shock promoter and that the conditions the cell is subjected to are hyperthermic conditions comprising a temperature between about 37°C and 42°C. Claim 34 has been canceled. Claims 35-37 depend on amended claim 33. Claim 38 is directed to a method of altering the genetic material of a mammal including, providing an expression construct with an inducible promoter linked to a gene encoding a transactivating factor, and a second promoter linked to a selected polynucleotide, wherein the second promoter is activated by the transactivating factor; and introducing the expression construct into a cell of the mammal. Applicants have amended claim 38 to specify that the inducible promoter is a heat shock promoter.

The Examiner holds that the specification does not enable a method of provoking an immune response in a mammal, a method of altering the genetic material of a mammal, or providing an expression construct comprising the inducible promoters, HSP28, HSP72 or HSP73. The Examiner asserts that the specification only provides working examples of transfecting two cell lines, *in vitro*, with expression constructs comprising a heat shock promoter, hsp70, wherein the heat shock promoter is induced in cells when the cells are subjected to hyperthermic conditions. Further, the Examiner protests that the experiments described in Examples 1-3 of the specification only provide data which indicates the relative inducibility of the heat shock promoter by measuring the amount of IL-2 expressed, and that there is no indication that the two cell lines, which can be considered tumor cell lines, are affected with respect to growth rates or display any changes which would be associated with an immune response which is elicited

by the selected polynucleotide. Thus, the Examiner appears to assert that the guidance in the specification is limited to HSP70 and the cell lines MCF7 and DU145, and therefore the specification does not teach how to provide an expression construct comprising the inducible promoters, HSP28, HSP72 or HSP73 or a method of provoking an immune response in a mammal. Applicants respectfully assert that the examples disclosed in the specification are not limited to HSP70 and the cell lines MCF7 and DU145, rather Applicants have chosen to exemplify the instant invention through HSP70 and these two specific cell lines. Again, Applicants refer the Examiner to page 33, lines 16-19, where the specification explicitly states that any inducible promoter may be used in the practice of the present invention and that all such promoters would fall within the spirit and scope of the claimed invention. As indicated above, Applicants have extensively described various promoters and promoter control regions (see page 29, section: f) Control Regions) and the use of the HSP70 promoter in order to induce expression of a reporter gene (see page 58, Example 1). Thus, Applicants assert that the skilled artisan would be capable of producing the claimed expression construct wherein the heat shock promoter is HSP28, HSP72 or HSP73 or provoke an immune response via the claimed expression construct, by following the guidelines provided in Applicants' specification. Moreover, the skilled artisan will be able to correlate the *in vitro* effect of the heat shock promoters of the instant invention with the *in vivo* effect of these heat shock promoters (see Example 4, re "Animal Studies", page 69). The Examiner has not supplied convincing reasons why one skilled in the art would not be able to do so in light of the teachings of the instant inventions. Applicants respectfully remind the Examiner that neither the inclusion of specific examples in the specification nor the disclosure of all possible embodiments is a prerequisite for enablement (MPEP 2164.02).

The Examiner states that at the time of filing, the art of gene therapy was known to be unpredictable and non-routine. The Examiner points to the "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" (published December 7, 1995), where Orkin and Motulsky

indicate that clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol. Applicants respond by reminding the Examiner that the instant application was filed in 1998 and that it is well know in the art that gene therapy has rapidly progressed since 1995 and continues to do so. More importantly, the question of "clinical efficacy" is not relevant with respect to the patent laws. The assessment of clinical efficacy is conducted by the FDA, not the PTO.

Applicants respectfully request that the rejection of claims 1, 7-15, 17-26, 33, and 35-38 under 35 U.S.C. § 112, first paragraph be withdrawn.

Claims 7, 38, and 41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states the following:

> Claims 7 and 41 are rendered vague and indefinite by the recitation of "HSP28", "HSP72" and HSP73" promoters as it is unclear what nucleic acid sequences are encompassed in these promoters as the promoter sequences are not defined in the specification nor in the prior art.
>
> Claim 38 is rendered vague and indefinite by the phrase "said selected polynucleotide" on line 5 as there is no previous recitation of a selected polynucleotide. The phrase lacks antecedent basis. The term "said" should be changed to "a to overcome this rejection.

Applicants have amended claim 38 to change "said selected polynucleotide" to "a selected polynucleotide" to comply with the Examiners suggestion.

The Examiner holds that claims 7 and 41 are rendered vague and indefinite by the recitation of "HSP28", "HSP72" and HSP73" promoters as it is unclear what nucleic acid sequences are encompassed in these promoters as the promoter sequences are not defined in the specification nor in the prior art. Applicants have pointed out (*supra*) that the guidelines provided with respect to HSP70 are applicable to

HSP28, HSP72, and HSP73. Moreover, Applicants are in possession of the necessary common features of the elements possessed by the promoters claimed in the instant invention, including HSP28, HSP72, and HSP73. Hence, Applicants assert that the claim language in claim 7 and 41 is supported by the specification. Applicants have also referred the Examiner to various references (*supra*) that further describe HSP72, HSP73, and HSP28 promoters. Applicants assert that the language of the claims is both clear and definite and one of ordinary skill in the art would readily be able to discern the scope and meaning of the claim as written. Claims 7 and 41 do not constitute flawed claims, rather they are broad claims. "Breadth of a claim should not be equated with indefiniteness." MPEP 2173.04, *In re Miller*, 169 USPQ 597 (CCPA 1971).

Applicants respectfully request reconsideration and withdrawal of the rejections of claims 7, 38, and 41 under 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. §102

Claims 1-7, 9, 10-12, 14, 16, 39-41, 43, 44, and 46 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bromley *et al.* (EP 0299127, 1989).

The rejection of claims 1-7, 9, 10-12, 14, 16, 39-41, 43, 44, and 46 is respectfully traversed.

The Examiner asserts that Bromley *et al.* disclose modified inducible hybrid genes, i.e., expression constructs, comprising genes of interest operably linked to HIV LTR promoter sequences and a tat-III gene operably linked to a heat shock promoter such as the hsp70 promoter. The Examiner further states that in Bromley *et al.* the hybrid genes can be part of one or separate vectors, and the inducible hsp promoter is activated by hyperthermic conditions wherein heat treatment occurs at 42.5°C or 43°C (which can be considered about 40°C or 41°C or 42°C). Applicants have amended claims 1, 5-7 and 39 accordingly.

Claims 2-4 have been canceled. Claims 5-7, 9, 10-12, 14 and 16 depend on amended claim 1. Claims 40 and 42 have been canceled. Claims 41, 43, 44 and 46 depend on amended claim 39.

Claim 1 is directed to a method of effecting expression of a selected polynucleotide in a mammalian cell which includes providing an expression construct with an inducible promoter linked to a gene encoding a transactivating factor, and a second promoter linked to the selected polynucleotide, wherein the second promoter is activated by the transactivating factor. The method further includes introducing the expression construct into the cell and subjecting the cell to conditions which activate the inducible promoter, resulting in the expression of the selected polynucleotide. Applicants have amended claim 1 to specify that the inducible promoter is a heat shock promoter. Applicants have further amended claim 1 to specify that the conditions that activate the heat shock promoter are hyperthermic conditions comprising a temperature between about 37°C and 42°C. Claims 5-7, 9, 10-12, 14 and 16 depend on amended claim 1. Applicants point the Examiner to page 3, lines 3-13 and page 16, lines 15-27 of the specification where the disclosure discusses in detail the advantages of the heat shock promoter of the instant invention, the main advantage being the activation of the heat shock promoter at temperatures below 42°C. Particularly, on page 16, line 27 and page 17, lines 1-4, Applicants emphasize that prior to the present invention, efficacy of hyperthermia required that temperatures within tumor(s) remain above about 43°C for 30 to 60 minutes while safety considerations limit temperatures in normal tissues to below 42°C. Furthermore, the disclosure explains that achieving uniform temperature above 42°C in tumors is difficult and not often possible. Applicants support their findings with working examples on page 61, lines 3-7, where the expression of EGFP is driven by the HSP70-derived promoter (results are shown in Figure 4). Applicants show that their heat shock promoter drives expression of EGFP at a temperature as low as 37°C. Additional working examples on page 66 (see Table 4) show that construct pf12 (see Figure 8) which includes the HSP70B promoter, tat, the HIV1 LTR, and the gene for IL-2, produced a 5-fold

expression increase of IL-2 at a temperature of 37°C compared to the CMV driven control. Moreover, at 39°C, pf12 produced 7-fold more IL-2 than the CMV driven controls at 37°C (see page 66, lines 3-10). Hence, Applicants have established that their heat shock promoter is indeed activated at basal temperatures, which is clearly novel and an unprecedented achievement.

"In order for a rejection under §102(b) to be valid, each and every element of the claim must be found in the prior art reference." *(MPEP 2131; In re Royka and Martin, 180 USPQ 580 (CCPA 1974)).*

Applicants further assert that while Bromley *et al.* claim that the hybrid genes can be part of one or separate vectors (see claim 5 in Bromley *et al.*), they neither disclose nor teach a construct where the hybrid genes are on one vector, thus, they do not enable one skilled in the art to make or use the same. More importantly, Bromley *et al.* teach a construct capable of expressing a tat-III gene segment (700 nt) under the control of a human hsp70 promoter, wherein the inducible hsp promoter is activated by hyperthermic conditions wherein heat treatment occurs at 42.5°C or 43°C (see Bromley *et al.*, page 5, lines 33-44). In comparison, the instant invention teaches various constructs including pC8, pf12, and p007 wherein each construct includes the minimal heat shock promoter upstream of either the tat gene or a multiple cloning site (MCS) in combination with either the HIV1 or HIV2 long terminal repeats (LTRs), and the mouse Interleukin-2 (IL-2) gene (see page 64, lines 6-12). The HIV tat gene of the instant invention spans 400 nt (see page 64, lines 22-24). Applicants refer the Examiner to Figure 8 for a summary of the constructs. As pointed out above, the heat shock promoter of the instant invention is activatable at basal temperatures.

"When a claimed invention is not identically disclosed in a reference, and instead requires picking and choosing among a number of different options disclosed by the reference, then the reference does not anticipate." *Mendenhall v. Astec Industries, Inc., 13 USPQ.2d 1913, 1928 (Tenn. 1988), aff'd, 13 USPQ.2d 1956 (Fed. Cir. 1989).*

Clearly, Bromley *et al.* fail to teach, either expressly or inherently, a method of effecting expression of a selected polynucleotide in a mammalian cell which includes providing an expression construct with a heat shock promoter linked to a gene encoding a transactivating factor, and a second promoter linked to the selected polynucleotide, wherein the second promoter is activated by the transactivating factor, and further includes introducing the expression construct into the cell and subjecting the cell to hyperthermic conditions comprising a temperature between about 37°C and 42°C which activate the heat shock promoter, resulting in the expression of the selected polynucleotide.

Claim 39 is directed to an expression construct including a gene encoding a transactivating factor, an inducible promoter linked to the gene, a selected polynucleotide, and a second promoter linked to the selected polynucleotide, wherein the second promoter is activated by the transactivating factor. Applicants have amended claim 39 to specify that the inducible promoter is a heat shock promoter which is activated at hyperthermic conditions comprising a temperature between about 37°C and 42°C. Claims 41, 43, 44 and 46 depend on amended claim 39. Applicants contend that the construct as amended differs from Bromley *et al.* for the same reasons specified above.

"Anticipation requires identity of invention. The claimed invention, as described in appropriately construed claims, must be the same as that of the reference in order to anticipate." *Glaverbel Societe Anonyme v. Northlake Marketing & Supply Inc., 45 F.3d 1550, 33 USPQ.2d 1496, 1498 (Fed. Cir. 1995).*

In light of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1, 7, 9, 10-12, 14, 16, 39, 41, 43, 44, and 46 under 35 U.S.C. § 102(b).

Claims 1, 10, 12, 13, 15, 16, 39, and 44-46 are rejected under 35 U.S.C. § 102(e) as being anticipated by Gage *et al.* (U.S. Patent No. 5,770,414, 1998, effective filing date of 2/20/96).

The Examiner states the following:

> Gage et al. disclose an expression construct comprising 1) an inducible promoter operably linked to a gene encoding a transactivating factor, 2) a second promoter operably linked to the selected polynucleotide which is a protein, wherein the second promoter is activated by the transactivating factor, 3) a gene encoding a selectable marker, 4) and an internal ribosome entry site positioned between a first and second selected polynucleotide (see, e.g., column 4, lines 21-65, column 5, lines 17-48, and Figure 1).

The rejection of claims 1, 10, 12, 13, 15, 16, 39, and 44-46 is respectfully traversed.

Applicants have amended claim 1 to specify that the inducible promoter is a heat shock promoter, and that the conditions that activate the heat shock promoter are hyperthermic conditions comprising a temperature between about 37°C and 42°C. Claims 10, 12, 13, 15, and 16 depend on amended claim 1. Applicants would like to draw the Examiner's attention to the fact that Gage *et al.* do not disclose a heat shock promoter. More specifically, Gage *et al.* discuss that a long terminal repeat (LTR) of Moloney murine sarcoma virus is preferably used for transcription of mRNA containing both, a tetracycline controlled transactivator (tTA) and a neomycin phosphotransferase gene (neo) by means of an internal ribosome entry site (IRES). Gage *et al.* further specify that other viral LTRs can be used (see US Patent No. 5,770,414; column 4, lines 54-60). Gage *et al.* do not teach the use of a heat shock promoter. Thus, the disclosure of Gage *et al.* does not anticipate the claimed invention.

Claim 39 has been amended to specify that the inducible promoter is a heat shock promoter which is activated at hyperthermic conditions comprising a temperature between about 37°C and 42°C. Claims 44-46 depend on amended claim 39. Applicants contend that the construct as amended differs from Gage *et al.* for the same reasons specified above. Hence, Gage *et al.* does not anticipate the claimed invention.

In light of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1, 10, 12, 13, 15, 16, 39, and 44-46 under 35 U.S.C. § 102(e).

Rejections Under 35 U.S.C. §103

Claims 1, 2, 7, and 39-41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bromley *et al.* (EP 0299127, 1989), taken with any one of Stover (U.S. Patent No. 5,583,038, 1996, filed 1992), Hickey *et al.* (Nucleic Acids Research, 14:4127-4145, 1986), Gaestel *et al.* (Gene, 128:279-283, 1993), Dale *et al.* (Gene, 172:279-284, 1996), or Quail *et al.* (EP 0342926, 1989).

The rejection of claims 1, 2, 7, and 39-41 is respectfully traversed.

As discussed above, with respect to the 35 U.S.C. § 102(b) rejections, Bromley *et al.* disclose modified inducible hybrid genes, i.e., expression constructs, comprising genes of interest operably linked to HIV LTR promoter sequences and a tat-III gene operably linked to a heat shock promoter such as the hsp70 promoter. The Examiner states that Bromley *et al.* do not disclose all of the claim-designated inducible promoters. Then the Examiner asserts that Stover discloses expression vectors comprising the hsp60 or hsp70 promoter operably linked to a gene of interest; that Hickey *et al.* disclose an expression construct comprising the human hsp27 promoter fragment operably linked to a polynucleotide encoding a gene of interest which is induced by heat shock; that Gaestel *et al.* disclose hsp25 and hsp27 promoter fragments which contain similar transcriptional regulatory elements including the putative heat shock element consensus sequence; that Dale *et al.* disclose an expression construct comprising the murin 84 kDa heat shock protein promoter, which is one of two genes which code for hsp90 proteins, operatively linked to a gene of interest, and which is induced by heat shock; and that Quail *et al.* disclose an expression construct comprising a ubiquitin promoter system, operably linked to a gene of interest, which is induced by heat shock. The Examiner opines that it would have been obvious to one of ordinary skill in the art at the time of filing to modify the expression construct of Bromley *et al.* by substituting the hsp70 promoter of Bromley *et al.* with the hsp60 promoter disclosed by Stover, or the hsp27 promoter disclosed by Hickey *et al.*, or the hsp25 or hsp27 promoters disclosed by Gaestel *et al.*, or the hsp90 promoter disclosed by Dale *et*

al., or the ubiquitin promoter disclosed by Quail *et al.* in view of the teachings of Bromley *et al.* that the hsp70 promoter can be substituted with hsp promoters obtained from hsp proteins of different molecular weights, or with other inducible promoters.

As already discussed, with respect to the 35 U.S.C. § 102(b) rejection, Applicants have amended claim 1 to specify that the inducible promoter is a heat shock promoter, and that the conditions that activate the heat shock promoter are hyperthermic conditions comprising a temperature between about 37°C and 42°C. These amendments clearly distinguish the invention from Bromley *et al.* for reasons discussed above (*supra*). Consequently, Bromley *et al.* is no longer a relevant reference in combination with the other references cited by the Examiner. Claim 2 has been canceled and claim 7 has been amended to depend on claim 1.

Heat shock promoters of the instant invention including HSP70, HSP90, HSP60, HSP27, HSP72, HSP73, HSP25, ubiquitin, and HSP28 that can be activated at temperatures as low as 37°C are clearly novel and unobvious. Hence, Applicants submit that the references of Bromley *et al.* and Stover, or Hickey *et al*, or Gaestel *et al.*, or Dale *et al.*, or Quail *et al.* can no longer be properly combined because there is no motivation in either the references themselves or in the knowledge generally available to one of ordinary skill in the art to combine them (MPEP 2143.01).

As discussed above, claim 39 has been amended to specify that the inducible promoter is a heat shock promoter which is activated at hyperthermic conditions comprising a temperature between about 37°C and 42°C. Claim 41 depends on amended claim 39. Claim 40 has been canceled. Applicants assert that the construct as amended differs from Bromley *et al.* for the same reasons specified above (*supra*). The Examiner does suggest that one of ordinary skill in the art would have had a high expectation of successfully modifying the expression construct of Bromley *et al.* to include any one of the known inducible promoters, as taught by Stover, Hickey *et al*, Gaestel *et al.*, Dale *et al.*, or Quail *et al.* without

undue experimentation. Applicants respectfully disagree and content that one of ordinary skill in the art would not be motivated to combine the references, as there is nothing in the references that teaches "any heat shock promoter that can be activated at temperatures as low as 37°C". Hence, there would be little motivation for the skilled artisan to combine the expression construct mentioned in Bromley *et al.* with any one of the inducible promoters taught by Stover, Hickey *et al*, Gaestel *et al.*, Dale *et al.*, or Quail *et al.* Even if the cited references were properly combined, the combination would still not render the present invention obvious. All limitation of the claims must be suggested by the combination of references cited as prior art in order to establish *prima facie* obviousness (MPEP 2143.03; *In re Royka and Martin*, 180 USPQ 580 (CCPA 1974)). As outlined above, all of the rejected claims 1, 7, 39 and 41 include as a limitation the requirement that the heat shock promoter be activated at hyperthermic conditions comprising a temperature between about 37°C and 42°C. As already discussed above, with respect to the 35 U.S.C. § 102(b) rejections, the construct disclosed by Bromley *et al.* is not identical to the claimed invention. Similarly, the other references such as Stover, Hickey *et al*, Gaestel *et al.*, Dale *et al.*, and Quail *et al.* teach or suggest nothing about a heat shock promoter that can be activated at temperatures as low as 37°C. Since in each case some of the claim limitations are not suggested by the cited combination of references, the rejection is no longer proper.

Thus, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1, 7, 39 and 41 under 35 U.S.C. § 103(a).

Claims 1, 8, 39, and 42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bromley *et al.* (EP 0299127, 1989), taken with either Webster *et al.* (U.S. Patent No. 5,834,306, 1998, effective filing date of 12/23/94) or Dachs *et al.* (Nature Medicine, 3:515-520, 1997).

This rejection is respectfully traversed.

The Examiner holds that it would have been obvious to one of ordinary skill in the art at the time of filing to modify the expression construct of Bromley *et al.* by modifying the inducible promoter to include a hypoxia responsive element as disclosed by Webster *et al.* or Dachs *et al.*, in view of the teachings of either Webster *et al.* or Dachs *et al.* that this element effectively modulates gene expression under hypoxic conditions. The Examiner further holds that one of ordinary skill in the art would have had a high expectation of successfully modifying the expression construct of Bromley *et al.* by including an additional regulatory element, such as the hypoxia-responsive element of Webster *et al.* or Dachs *et al.*, to produce an expression construct, for the purpose of providing a construct, which can be regulated by a variety of environmental/physiological conditions, without undue experimentation, barring evidence to the contrary.

Claims 1 and 39 have been amended to specify that the inducible promoter is a heat shock promoter which is activated at hyperthermic conditions comprising a temperature between about 37°C and 42°C (*supra*). Applicants point the Examiner to the previous discussions (*supra*) where applicants have discussed in detail why Bromley *et al.* is not identical to the instant invention. Claim 8, drawn to a method of claim 1, wherein said inducible promoter comprises a hypoxia-responsive element, has been canceled. Claim 42, drawn to the expression construct of claim 39, wherein said inducible promoter comprises a hypoxia-responsive element, has been canceled.

Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1 and 39 under 35 U.S.C. § 103(a).

Claims 1, 10, 11, 39, and 44 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bromley *et al.* (EP 0299127, 1989), taken with any one of Dubensky, Jr. *et al.* (U.S. Patent No. 5,814,482, 1998, effective filing date of 9/14/94), Scott *et al.* (WO 95/09913, 1995), Saito *et al.* (U.S. Patent No. 5,817,492, 1998, effective filing date of 8/30/95), Weinberg *et al.* (WO 89/10412, 1989), Beach *et al.* (U.S.

Patent No. 5,889,169, 1999, effective filing date of 5/25/94), or Tewari *et al.* (Biochim. Biophys. Acta, 1209:293-295, 1994).

This rejection is respectfully traversed.

The Examiner holds that it would have been obvious to one of ordinary skill in the art at the time of filing to modify the expression construct of Bromley *et al.* by substituting one polynucleotide encoding a protein of interest with another polynucleotide encoding a protein of interest, such as those disclosed by Dubensky, Jr. *et al.* (IL-1, IL-2, IL-4, IL-7, IL-12, IL-15, IFN alpha or gamma, G-CSF, GM-CSF, TNF, ICAM-1, Flt-3 ligand, HSV-tk, antisense polynucleotides including antisense thymidine kinase, antisense dihydrofolate reductase, antisense HER2, antisense ABL, and antisense Myc, and ribozymes), the polynucleotide encoding TIMP-3, as disclosed by Scott *et al.*, or any of the polynucleotides disclosed by Saito *et al.*, such as HLA-B7 or p53, the neu polynucleotide disclosed by Weinberg *et al.*, the p16 polynucleotide disclosed by Beach *et al.*, or the ornithine decarboxylase antizyme polynucleotide disclosed by Tewari *et al.* in view of the teachings of Bromley *et al.* that different numerous genes of interest and products of clinical and pharmaceutical interest can be readily incorporated into the expression construct. The Examiner further holds that the skilled artisan would have been motivated to use the expression construct of Bromley *et al.* for producing large quantities of protein in view of the advantages disclosed by Bromley *et al.* in using such an expression construct.

Although Applicants disagree with the Examiner that one skilled in the art would have been motivated to use the expression construct of Bromley *et al.* for producing large quantities of protein, Applicants' traversal does not merely rely on this disagreement. Rather, Applicants contend that the construct disclosed in Bromley *et al.* is not identical to the instant invention (*supra*). Applicants reiterate that the heat shock promoter of the instant invention can be activated at temperatures as low as 37°C which is clearly novel and unobvious over the existing prior art. Claims 1 and 39 have been amended to specify

that the inducible promoter is a heat shock promoter which is activated at hyperthermic conditions comprising a temperature between about 37°C and 42°C (*supra*). Claims 10 and 11 depend on amended claim 1 while claim 44 depends on amended claim 39. Thus, the skilled artisan could not have been motivated to use the expression construct of Bromley *et al.* in order to produce large quantities of protein at temperatures as low as 37°C to 42°C.

"Focusing on the obviousness of substitutions and differences instead of the invention as a whole is a legally improper way to simplify the difficult determination of obviousness. Arguing that "it would be obvious," rather than that "it would have been obvious," shifts the court's focus to the wrong period of time; namely, to a time long after the invention was made, in which, more likely than not, the prior art and the level of ordinary skill in the art are more advanced. *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986)."

Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1, 10, 11, 39 and 44 under 35 U.S.C. § 103(a).

Claims 1 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bromley *et al.* (EP 0299127, 1989), taken with either of Loeb *et al.* (U.S. Patent No. 5,877,010, 1999, effective filing date of 5/2/95), Hancock (in Methods in Molecular Biology, 8, Practical Molecular Virology, Viral Vectors for Gene Expression, ed. M. Collins, Humana Press Inc., Clifton, New Jersey, 1991, Chapter 14, pages 164-165) or Talavera *et al.* (in Methods in Molecular Biology, 8, Practical Molecular Virology, Viral Vectors for Gene Expression, ed. M. Collins, Humana Press Inc., Clifton, New Jersey, 1991, Chapter 21, pages 235-248).

This rejection is respectfully traversed.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time of filing to modify the method of Bromley *et al.* of introducing an expression construct into a cell by utilizing any of the well known gene transfer methodologies established in the art of molecular biology. The Examiner states that utilizing the gene transfer systems such as herpes simplex viral vectors, adenoviral vectors, adenovirus-associated viral vectors, pox vectors, parvoviral vectors, baculovirus vectors, and retroviral vectors disclosed by Loeb *et al.*, or the liposome-based delivery system disclosed by Hancock, or the vaccinia virus-based delivery system of Talavera *et al.*, would have been obvious and well within the purview of one of ordinary skill in the art of molecular biology.

Claim 1 has been amended to specify that the inducible promoter is a heat shock promoter which is activated at hyperthermic conditions comprising a temperature between about 37°C and 42°C (*supra*).

Claim 15 is dependent on the method of claim 1, wherein the introduction of said expression construct into said cell is mediated by a delivery vehicle selected from the group consisting of liposomes, retroviruses, adenoviruses, adeno-associated viruses, lentiviruses, herpes simplex viruses, and vaccinia viruses. Applicants assert that it would not have been obvious to the skilled artisan to modify the method of Bromley *et al.* of introducing an expression construct into a cell by utilizing any of the gene transfer systems disclosed by Loeb *et al.*, Hancock, or Talavera *et al.* in order to achieve expression of a selected polynucleotide via activation of a heat shock promoter at temperatures as low as 37°C to 42°C. Since Bromley *et al.* does not anticipate the instant invention (*supra*), Applicants submit that the references of Bromley *et al.*, and Loeb *et al.*, or Hancock, or Talavera *et al.* can not be properly combined because there is no motivation to combine them other than the teachings derived from the instant invention.

"When prior art references require a selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself. Something in the prior art as a whole must suggest the desirability, and thus the

obviousness, of making the combination. *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988)."

Applicants emphasize that prior to the instant invention, approaches of using heat shock promoters to drive the expression of transactivating proteins to conditionally express other promoters differed, the most important difference being the need for induction temperatures of greater than 42°C (see page 13, lines 16-27). Applicants have achieved the induction of the claimed heat shock promoters at temperatures as low as 37°C (*supra*). The Examiner points to nothing in the cited references that discusses the use of the delivery vehicles at specific temperatures, let alone at temperatures between 37°C and 42°C. Furthermore, Applicants are able to show a clear distinction in the expression levels resulting from their approach (see page 14, lines 1-2 and page 65, "Heat-Induced Amplification Studies"). Thus, neither Bromley *et al.* nor the combination of Bromley *et al.*, and Loeb *et al.*, or Hancock, or Talavera *et al.* could have taught the superiority of the claimed expression constructs containing the heat shock promoters, or the methods of effecting expression via these expression constructs for any type of expression.

In light of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1 and 15 under 35 U.S.C. § 103(a).

Objections

The disclosure is objected to because of informalities relating to Tables 5 and 6. According to the Examiner, in Table 5 on page 67, it is not apparent what the numbers in parentheses represent, and in Table 6 on page 68, it is unclear what the dashes mean. The numbers in parentheses in Table 5 on page 67 have been removed. The use of the dashes in Table 6 on page 68 has been clarified by adding the following text to Table 6: "the dashes represent insufficient data points".

Sequence Compliance

The Examiner holds that the application fails to comply with the requirements of 37 CFR 1.821(d) as reference must be made to the sequence disclosed in Figure 10, either in the figure or in the text of the description of the figure, by use of the sequence identifier, preceded by "SEQ ID NO.". Applicants point the Examiner to page 58, lines 13-14 of the specification, where Applicants state the following: "M5 was constructed by replacing the CMV promoter in pcDNA3.0 (Invitrogen, Inc.) with a minimal HSP70B promoter (**SEQ ID NO:1, Figure 10**), a 0.4 kb fragment (HindIII-BamH1) of the human heat shock protein 70B (HSP70B) promoter, obtained from StressGen, Inc. Hence, Applicants have made reference to the sequence disclosed in Figure 10 via the sequence identifier (i.e., SEQ ID NO:1) in the text of the description of Figure 10.

Conclusion

Reconsideration of claims 1,5-7, 9-26, 33, 35-39, 41, and 43-46 in view of the foregoing amendments and remarks, and an early indication of their allowability, are earnestly solicited.

Respectfully submitted,

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